

# Five-year Findings of a Comparison of Ambulatory Short Course Chemotherapy with Radical Surgery Plus Chemotherapy for Tuberculosis of the Spine in Madras

A.M. REETHA, S. SIVASUBRAMANIAN, R. PARTHASARATHY, P.R. SOMASUNDARAM, R. PRABHAKAR

*Tuberculosis Research Centre, Madras*

A controlled clinical trial was undertaken to compare the efficacy of short course chemotherapy given alone or combined with radical surgery in the treatment of spinal tuberculosis without paraplegia. Patients with active spinal tuberculosis involving the vertebral bodies and without paraplegia were randomly allocated to one of the following three regimens.

- (a) Rad 6 : Radical anterior resection with bone grafting plus six months of daily isoniazid and rifampicin.
- (b) Amb 6 : Ambulatory chemotherapy with six months of daily isoniazid and rifampicin, without surgery.
- (c) Amb 9 : Same as (b) but the duration being nine months.

The patients were intensively followed up for five years from the start. At five years, 98% of 86 Amb 9, 91% of 82 Amb 6 and 88% of 82 Rad 6 patients had a favourable status. It is concluded that ambulatory chemotherapy for 6 or 9 months is highly effective in the treatment of spinal tuberculosis. Radical surgery did not enhance the efficacy of the short course regimen.

Controlled clinical trials of the Medical Research Council Working Party on Tuberculosis of the Spine clearly showed that ambulatory out-patient chemotherapy with daily isoniazid plus PAS for 18 months was highly effective in the treatment of spinal tuberculosis (MRC-1973 a and b, 1974 a, 1976, 1978, 1985). Further, there was no additional benefit because of rest in bed (MRC-1973 a, 1976, 1985), or a plaster-of-Paris jacket (MRC-1973 b, 1976, 1985), or a simple debridement operation (MRC-1974 a, 1978). On the contrary, the modified Hong Kong operation (i.e. radical resection of the tuberculous focus and anterior spinal fusion) was not only highly effective but also conferred special benefits, namely early healing by bony fusion, less spinal deformity and rapid resolution of mediastinal abscesses (MRC-1974 b, 1978). However,

it is a major surgical procedure requiring surgical expertise, efficient nursing, excellent anaesthetic facility and abundant resources, which are not widely available in developing countries.

Short course regimens based on isoniazid and rifampicin for 6-9 months have been shown to be highly effective in sputum positive pulmonary tuberculosis (BMRC-1974 and 1976; Fox, 1981; IUAT, 1988), and the bacillary population in spinal disease is much smaller than in pulmonary lesions (Canetti et al, 1957; Debeaumont, 1966). Hence a controlled clinical trial was undertaken in Madras, India, in collaboration with British Medical Research Council Working Parties on Tuberculosis of the Spine to compare the efficacies of 6 or 9 months of ambulatory chemotherapy with isoniazid plus rifampicin daily and radical surgery plus the above chemotherapy for 6 months on an out-patient basis. The findings up to 3 years have already been reported (ICMR, 1989). Results up to 5 years are presented here.

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A.M. Reetha, S. Sivasubramanian, R. Parthasarathy,  
P.R. Somasundaram, R. Prabhakar  
Tuberculosis Research Centre, Mayor Ramanathan Road  
(Spartank Road), Chetput, Madras 600031

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Correspond with : R. Prabhakar, Director.

## MATERIAL AND METHODS

*Eligibility Criteria for Admission to Study*

Patients with clinically and radiographically active spinal tuberculosis involving any vertebral body from the first thoracic to the first sacral, inclusive, were eligible for admission to the study. Patients were ineligible if they had (a) paralysis of the lower limbs severe enough to prevent them from walking across a room (about 6 meters), (b) serious extra-spinal disease, tuberculous or non-tuberculous, (c) a history of previous chemotherapy for 12 months or more, or (d) already had major surgery for their spinal tuberculosis.

*Pre-treatment Investigations*

Investigations on admission included the following:

(a) Complete clinical (including neurological) examination, (b) antero-posterior (A-P) and lateral radiographs of the whole spine and a postero-anterior (P-A) radiograph of the chest, (c) examination by culture of (i) two specimens of pus from any abscess or sinus, if present and (ii) 3 sputum specimens from patients with radiographic evidence of pulmonary tuberculosis and (d) sensitivity tests to isoniazid and rifampicin on positive cultures of *M. tuberculosis*.

*Allocation to Treatment*

Each patient was allocated at random to one of the following 3 treatment series :

- (a) Rad 6 : Radical anterior resection with bone grafting plus isoniazid and rifampicin in 1 dose daily for 6 months.
- (b) Amb 6 : Ambulatory treatment with isoniazid and rifampicin in 1 dose daily for 6 months.
- (c) Amb 9 : Same as (b), but the duration being 9 months.

The dosages were 5-7 mg/kg body-weight for isoniazid and 10-15 mg/kg for rifampicin (ICMR-1989).

*Assessment of Progress*

Progress was assessed at 6 monthly intervals from 3-5 years and was based on : (1) clinical (including neurological) examination, (2) A-P and lateral radiographs of the vertebrae involved, and a P-A radiograph of the chest if lungs were affected prior to admission, and (3) bacteriological examination of pus from any sinus or abscess, and of sputum from patients with pulmonary tuberculosis.

## RESULTS

*Study Population*

In all, 304 (100 Rad 6, 101 Amb 6, 103 Amb 9) patients were admitted to the study. For various reasons, 54 (18 Rad 6, 19 Amb 6, 17 Amb 9) patients were excluded from analyses. The reasons for the exclusions of 44 patients were given in the 3-year report (ICMR-1989). The other ten patients (3 Rad 6, 1 Amb 6, 6 Amb 9) were excluded during the 3-5 year period because 5 (1 Rad 6, 4 Amb 9) died of non-tuberculous causes, 4 (2 Rad 6, 2 Amb 9) had additional treatment for extra-spinal tuberculosis and 1 (Amb 6) was lost to follow-up; thus, there remained 250 (82 Rad 6, 82 Amb 6, 86 Amb 9) patients in the analyses.

*Intensity of Follow-up*

the intensity of follow-up examinations during the 5 years was very high and similar in the 3 series. Thus, 99.5% of the Rad 6 and 100% of the combined Amb series patients were examined at 2 years after the start of treatment. The corresponding figures at 3 years were 98.5% and 98.8%, respectively, and at 5 years they were 97.9% and 100%, respectively. This has been achieved because of intensive efforts made by the staff to retrieve defaulters (Thilakavathi et al, 1993).

*Pre-treatment Characteristics*

The distributions of the clinical, radiographic and bacteriological findings before the start of treatment were broadly similar for the 2 series (Table 1). In brief, 34% of the 250 patients were aged less than 15 years and 25% were aged 35 years or more; 20% had a sinus and/or clinically evident abscess, 84% had an obvious kyphosis and 50% had lesions at the thoracic or thoraco-lumbar regions of the spine.

*Deaths*

Four patients (all Rad 6) died due to reasons associated with spinal tuberculosis, including 2 in the immediate post-operative period (ICMR-1989).

*Modification of the Allocated Treatment*

Major modifications were made to the allocated regimen in 11 patients (5 Rad 6, 5 Amb 6, 1 Amb 9). Of the 5 Rad 6 patients, the operation was abandoned in 2, the third had a second operation because of posterior displacement of the graft, the fourth had the graft removed for a persistent post-operative sinus and the fifth had additional drugs for myelopathy with complete paralysis,

and died in the 5th month. Of the ambulatory series patients; 4 (3 Amb 6, 1 Amb 9) had decompression surgery because of myelopathy with increasing functional impairment and 2 (both Amb 6) had additional chemotherapy because they developed clinically evident abscesses.

**Table 1 :** Pre-treatment characteristics

Pretreatment characteristics	Percentage of patients			
	Rad 6	Amb 6	Amb 9	Total
Age (years)				
0 - 4	11	17	13	14
5 - 14	20	27	14	20
15 - 34	43	39	43	42
35 - 54	26	13	26	22
55 or more	1	4	5	3
Sinus and/or clinically-evident abscess	20	26	14	20
Kyphosis	84	85	81	84
Limitation of movement	96	91	97	95
Myelopathy (Independent assessment)*	5	6	9	7
Site of lesion @				
Thoracic	34	37	41	37
Thoraco-lumbar	15	15	10	13
Lumbar	44	44	40	42
Lumbo-sacral	7	5	9	7
Mediastinal or psoas abscess shadow@	57	56	57	57
Total patients	82	82	86	250

\* On admission or within first 2 months of chemotherapy

@ Independent radiographic assessments (GW)

*Re-treatment during Follow-up Period*

No patient had reactivation of the spinal lesion during the five-year period of follow-up.

*Sinuses and/or Clinically-evident Abscesses*

In all, 49 (20% - 16 Rad 6, 21 Amb 6, 12 Amb 9) of the 250 patients had one or more sinuses and/or clinically evident abscesses on admission. By the end of treatment, the sinus and/or abscess had resolved in 15 of the 16 patients in the Rad 6 series and 29 of the 33 in the

combined ambulatory series. The resolution was slower in the two ambulatory series. By 21 months all 49 had resolved, without additional chemotherapy or surgery.

Sinuses and/or clinically evident abscesses were observed for the first time after the start of chemotherapy in 32 (5 Rad 6, 12 Amb 6, 15 Amb 9) patients. The difference between the Rad 6 and the combined ambulatory series was significant (P=0.05). Of these, the lesions in 22 (4 Rad 6, 6 Amb 6, 12 Amb 9) patients had resolved by the end of treatment and in all by 60 months. The detailed findings are reported elsewhere (16).

*Mediastinal Abscesses*

A total of 66 patients (20 Rad 6, 22 Amb 6, 24 Amb 9) had radiographically visible mediastinal abscesses on admission but no clinical evidence of sinus or abscess at any time during the five-year period. The abscesses had resolved without any intervention by 3 months in 13, 6 and 4, respectively, by 36 months in all except 3 (1 Amb 6, 2 Amb 9) and in 1 more (Amb 6) by 60 months (Rani et al, In Prep.).

*Nervous System Involvement*

Patients with myelopathy (defined as damage to or disease of the spinal cord) secondary to the spinal lesion were classified as having (a) functional impairment, or (b) no functional impairment (i.e. with abnormal physical signs only). Myelopathy was present on admission or developed within the first 2 months in 17 (7%) patients (4 Rad 6, 5 Amb 6, 8 Amb 9) including 11 (2 Rad 6, 5 Amb 6, 4 Amb 9) who had functional impairment.

The myelopathy resolved completely without additional chemotherapy or surgery in 11 (2 Rad 6, 2 Amb 6, 7 Amb 9), and resolved by 36 months with additional surgery with or without chemotherapy in 4 (3 Amb 6, 1 Amb 9); 1 (Rad 6) patient died with persisting functional impairment and in 1 (Rad 6) the myelopathy initially resolved by 9 months, recurred without functional impairment but again resolved by 42 months. Thus all 16 patients alive at 5 years had no myelopathy for the first time 2 months after the start of treatment but it had resolved by 42 and 15 months, respectively.

*Bony Fusion*

The rate of occurrence of bony fusion was similar in the 3 series. In approximately two-thirds of the patients, there was complete bony fusion by 36 months (Table 2). At 5 years, 77%, 75% and 74% had complete bony fusion, 21%, 15% and 18% had partial fusion and 3%, 10% and

**Table 2 :** Cumulative occurrence of complete bony fusion

Trt. series	Pts. assessed	Complete bony fusion (months)										Partial fusion at 60 months		No fusion at 60 months	
		0—12		0—24		0—36		0—48		0—60		No.	%	No.	%
		No.	%	No.	%	No.	%	No.	%	No.	%				
Rad 6	77	26	34	42	55	50	65	53	69	59	77	16	21	2	3
Amb 6	77	26	33	41	52	52	66	55	70	59	75	12	15	8	10
Amb 9	85	25	29	43	51	49	58	56	66	63	74	15	18	7	8

8% had no fusion, respectively, in the Rad 6, Amb 6 and Amb 9 series.

*Vertebral Body-loss*

On admission, the mean total vertebral body loss was 0.77 in 75 Rad 6, 0.83 in 75 Amb 6 and 0.65 in 82 Amb 9 patients (Table 3). The mean increase in vertebral body loss was 0.18, 0.34 and 0.24, respectively, in the 3 series during the 5-year period, indicating more loss of vertebral bodies in the two ambulatory series than in the surgical series, the difference being statistically significant (P=0.02).

*Angle of Kyphosis*

Regarding the angle of kyphosis on admission, the mean angle was 26.5° for 34 Rad 6, 28.2° for 45 Amb 6 and 25.2° for 50 Amb 9 patients in the 3 series (Table 3) which increased by 10.0°, 11.9° and 10.7°, respectively, during the course of five years. Thus the increases in the angle of kyphosis were similar, indicating no benefit by surgery.

*Status at 60 months*

At 60 months, 72 (88%) of the 82 Rad 6, 75 (91%) of the 82 Amb 6 and 84 (98%) of the 86 Amb 9 patients were classified as having a favourable status, that is, they had no sinus or clinical abscess present, no myelopathy and had had no additional operation or chemotherapy and no modification of the allocated regimen; they also had no limitation of physical activity due to the spinal lesion and their disease was radiographically quiescent (Table 4). The result in the Amb 9 series is significantly better than in the Rad 6 series (P=0.03). A further 2%, 2% and 1%, respectively, were clinically favourable but were classified as still not favourable solely because radiographically their disease was not yet considered to be quiescent. Eight (10%) of 82 Rad 6 patients were classified as unfavourable as compared with 5 (6%) of 82 Amb 6 and 1 (1%) of 86 Amb 6 patients, the total with an unfavourable status being 14 (6%) of the 250 patients. The 2 Rad 6 patients in whom operation had been abandoned for technical reasons died in the 25th

**Table 3 :** Assessments of total vertebral body loss and angle of kyphosis

Assessment	Site of lesion	Regimen	Total Pts.	Mean vertebral body loss/ angle of kyphosis on admission	Mean increase in vertebral body loss/angle during (months)		
					0—36	36—60	0—60
Total vertebral body loss	Any	Rad 6	75	0.77	0.18	0.00	0.18
		Amb 6	75	0.83	0.30	0.04	0.34
		Amb 9	82	0.65	0.20	-0.03	0.24
Angle of kyphosis*	Thoracic of thoraco lumbar	Rad 6	34	26.5°	10.2°	-0.2°	10.0°
		Amb 6	45	28.2°	13.5°	-1.6°	11.9°
		Amb 9	50	25.2°	10.0°	0.7°	10.7°

\* Patients with lordotic angles or with a lesion extending below L2 are not included.

and 28th months, both from non-tuberculous causes and with a favourable status at the last attendance before death.

**Table 4 :** Status at 60 months

	Rad 6		Amb 6		Amb 9	
	No.	%	No.	%	No.	%
Favourable*	72	88	75	91	84	98
Still not favourable						
Not quiescent radiographically	2	2	2	2	1	1
Unfavourable						
Death due to or associated with spinal tuberculosis @	4		0		0	
Additional surgery	2		1		1	
Additional surgery and chemotherapy	0	10	2	6	0	1
Additional chemotherapy	0		2		0	
Radical operation abandoned for technical reasons	2		0		0	
Tpta;	82	100	82	99	86	100

\* As defined in the text (page 9)

@ Including one patient who had additional chemotherapy for myelopathy and later died because of causes associated with spinal tuberculosis.

*Progress of Patients Excluded from the Main Analyses*

A total of 54 patients were excluded from the main analyses. Of these, 41 were considered to have evidence of active spinal tuberculosis. Seventeen patients were not followed up to five years (14 died from other causes with no evidence of activity of the spinal disease at the last assessment, 2 had refused surgery, 1 defaulted).

Of the other 24 patients, 16 (7 Rad 6, 4 Amb 6, 5 Amb 9) had an uneventful progress during the 5 years. In the remaining 8 (3 Rad 6, 2 Amb 6, 3 Amb 9) treatment was changed in 1 (hepatic toxicity) and the allocated chemotherapy was extended in 2 (tuberculosis of the hip-1; active paraplegia-1). The remaining 5 patients had treatment re-started during 3 to 5 years, 1 for reactivation

of spinal tuberculosis, and 4 for extra-spinal tuberculosis, namely, pulmonary tuberculosis-2; cervical-1 and mesenteric adenitis-1.

**DISCUSSION**

An earlier publication from this Centre (ICMR, 1989) had reported the results up to 3 years of ambulatory chemotherapy with daily isoniazid plus rifampicin for 6 or 9 months compared with the same chemotherapy for 6 months combined with radical resection (the modified ‘‘Hong Kong’’ operation) in the treatment of spinal tuberculosis. In brief, at 3 years, ambulatory chemotherapy for 9 months gave the best results, 96% of 92 Amb 9 patients attaining a favourable status, compared with 80% of 85 Rad 6 (P=0.003) and 87% of 83 Amb 6 patients (P=0.07). In all, only 15 (6%) of a total of 260 patients, belonging to all 3 series, had an unfavourable status.

At five years, 98% of 86 Amb 9, 91% of 82 Amb 6 and 88% of 82 Rad 6 patients had a favourable status, the difference between the Amb 9 and the Rad 6 series being significant (P=0.03). In all, 14 (6%) of the 250 patients in the 3 series were classified as having an unfavourable response. More importantly, 4 (5%) of 82 Rad 6 patients died due to reasons associated with their spinal disease, compared with none of 168 patients of the two ambulatory series combined. Thus the promising results at 3 years were maintained or improved at 5 years. The two ambulatory regimens were highly effective in the treatment of spinal tuberculosis, and apparently radical surgery did not enhance the efficacy.

Studies conducted in Korea and Rhodesia showed that ambulatory chemotherapy for 18 months with daily isoniazid plus PAS (with or without an initial streptomycin supplement) was very effective, 87% of 250 patients having a favourable status at 5 years (MRC-1976, 1978). In a concurrent comparison in Korea, a favourable status on the allocated regimen was observed in 82% of 65 and 75% of 71 with 6- and 9- month regimens of isoniazid plus rifampicin daily, respectively, compared with 79% of 67 with an 18-month regimen of isoniazid plus PAS or ethambutol daily (MRC-1993). It may be concluded that ambulatory chemotherapy for 6 or 9 months with daily isoniazid plus rifampicin is as highly effective as ambulatory chemotherapy for 18 months with daily isoniazid plus PAS.

The radical surgery has been investigated in studies at Hong Kong. It was combined with 18 months of daily isoniazid plus PAS supplemented with daily streptomycin

for 3 months (1st study) or with a 6- or 9-month regimen, the regimens being similar to the Rad 6 of the present study, but supplemented with twice-weekly streptomycin for 6 months and the duration of the latter regimen being 9 months (2nd study). The overall results were excellent in both the studies, 89% of 61 patients on the 18-month regimen, and 96% of 50 patients on the 6- and 9- month regimens combined having a favourable status at 5 years, respectively, on the allocated regimen (MRC-1978, In Prep.). Further, there were no deaths due to spinal disease among a total of 112 patients who had this surgery.

Considering the Hong Kong patients, who underwent radical surgery, complete bony fusion occurred in 92% of 60 patients by 5 years (1st study-18 month regimen) and in all (100%) of 50 patients of the 6- and 9- month regimens combined (2nd study -MRC-1978, In Prep.).

In the present study the only benefits conferred by the radical surgery were associated with sinus and/or clinically evident abscess and mediastinal abscess. The speed of resolution of these lesions was significantly greater in the surgery series than in the two ambulatory series (Rani et al, In Prep.). Moreover, the incidence of sinus and/or clinically evidence abscess was significantly less in the Rad 6 than in the combined Amb series ( $P=0.05$ ). Similar observations were made regarding sinuses and/or clinically evident abscesses in studies conducted in Korea and elsewhere, the chemotherapy being 18 months of daily isoniazid plus PAS (MRC-1973 a, 1974 a, 1974 b). These findings suggest that though radical surgery did not increase the proportion with a favourable status, it resulted in some benefits.

Patients with myelopathy severe enough to prevent them from walking across a room (about 6 meters) were not admitted to the study. However, those with paraparesis (but still able to walk) were admitted. In all, 19 (8%) of 250 patients had myelopathy either initially (17 patients) or developed it subsequently (2 patients) in the 5-year period. Myelopathy resolved in 14 patients on the allocated regimen and in 4 (3 Amb 6, 1 Amb 9) after additional surgery or chemotherapy; the other patient died with functional impairment. Other studies have shown that of 41 patients receiving 18 months of chemotherapy and having myelopathy during a 5-year period, the lesion resolved in 36 (MRC-1976, 1978), including 27 on the allocated regimen.

To sum up, when assessed at 5 years, ambulatory chemotherapy with daily isoniazid and rifampicin for 6 or 9 months was highly effective in spinal tuberculosis, a

favourable status on the allocated regimens being observed in 91% and 98%, respectively. Radical surgery did not enhance the efficacy. It may be concluded that spinal tuberculosis can be successfully treated in the great majority of patients with short-course chemotherapy on an out-patient basis. Radical surgery, if at all necessary for a select few, can be done in specialised spinal centres, where all facilities are available. These findings are of great relevance to the developing countries.

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